REMARKS

Claim 61 was pending and claim 56 was withdrawn in this application. The Examiner withdrew the Restriction Requirement dated February 2, 2003 (Paper No. 12), and rejoined claim 56 with claim 61 for examination. Thus, claims 56 and 61 are currently pending. No claim has been allowed.

Formal Matters

Applicants gratefully acknowledge the entry of the After Final Response (Paper No. 15) and the withdrawal of finality for the Action mailed June 12, 2003 (Paper No. 14).

Applicants also gratefully acknowledge the rejoining of claim 56 with claim 61.

Rejection under 35 U.S.C. § 102 (b)

Claims 56 and 61 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Kleinerman et al. (1989) or Kleinerman (1992). According to the Examiner, Kleinerman (1989) and Kleinerman (1992) teach a method of treating cancer patients comprising administering a pharmaceutical composition of MTP-PE encapsulated in multilamellar liposomes wherein the patients had been treated with antitumor therapy. The Examiner argues that the method of the prior art comprises the same method steps as claimed in the instant invention, and therefore would inherently lead to the amelioration of mucositis, myelosuppression, and peripheral neuropathy in the subset of patients that present with these conditions. The Examiner maintains that the subset of patients that have been treated with an anti-neoplasia agent would have these conditions, and thus the claimed population and a subset of the prior art population are the same. The Examiner further asserts that *Novitiski* supports the rejection of anticipation. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the methods disclosed in the Kleinerman publications fail to anticipate the claimed methods because neither publication teaches or suggests the use of MTP-PE to ameliorate the side effects of treatment with a second neoplastic agent. The underlying assumption the Examiner appears to be relying on is that the population of subject treated with a second neoplastic agent is the same population with mucositis. However, not every individual that is treated with a neoplastic agent develops mucositis nor does every neoplastic agent cause mucositis. Approximately 40% of patients receiving chemotherapy or radiotherapy develop oral mucositis. *See* Exhibit A, at page 2881. The risk factors for developing mucositis include age, gender, preexisting dental hygiene, nutritional status, as well as oral care during treatment. *See* Exhibit A, at page 2882-3 and Table 55.2-4. Moreover, the type of chemotherapeutic agent employed, the dose administered, and the schedule of dosing affect the risk of developing mucositis. *See* Exhibit A, at page 2883, Tables 55.2-3 and 55.2-4. Therefore, it is only the discrete subset of patients that develop or are at risk for mucositis that would benefit from the treatment of the claimed methods. Even in cases where patients do develop mucositis, it is not necessarily a sustained disease state. *See* Exhibit A, at page 2882 (discussing healing phase of mucositis as occurring from days 12-16 post-treatment). In most cases, mucositis resolves through a healing process, and therefore can be completely absent even from patients that have received high doses or long regimens of anti-neoplastic agents. Therefore, mucositis is <u>not</u> an inherent side effect of treatment with a second neoplastic agent. Because mucositis is not inherent in the patients receiving anti-neoplastic agents, neither publication of Kleinerman anticipates the claimed methods.

Moreover, neither Kleinerman publication teaches or suggests the administration of MTP-PE to a patient that is undergoing treatment with an anti-neoplastic agent as in the method of claim 56. In point of fact, both Kleinerman publications <u>teach away</u> from such co-administration by the express teaching of administration of MTP-PE alone. Therefore, neither publication anticipates the method of claim 56.

Furthermore, the holding in *Ex parte Novitiski*, 26 U.S.P.Q.2d 1389 (BPAI 1993) is inapposite to the instant methods because mucositis does not inherently result from treatment by a neoplastic agent. The court in *Novitiski* unmistakably distinguished the fact situation at issue, saying the claims at issue "do not specify any degree of nematode-inhibiting activity, or any level of protection from plant pathogenic nematodes." *See* Novitiski, at 1391. In other words, there was no requirement in these claims that the plant actually be infected by nematodes as there is a requirement in the instant methods that the patients have mucositis or be receiving treatment with a second neoplastic agent known to induce mucositis, *e.g.*, a toxic dose. The instant methods do expressly specify the patient population to be treated with the claimed methods, and therefore implicitly specify the degree of toxicity in the anti-neoplastic regimen experienced by this population. It must be sufficient to induce mucositis. Mucositis occurs in a discrete subset of patients receiving anti-neoplastic therapy, and it is this population that is treated using the claimed methods.

Moreover, the anti-mucositis effects are observed at dosage levels of MTP-PE that are insufficient to treat neoplastic disease. Applicants provided objective evidence of the anti-mucositis effects of MTP-PE in the example section of the instant specification. For example, in Table 7, the results from an experiment performed with MTP-PE and a second neoplastic agent are shown. In this experiment, the human colon carcinoma cell line CT-26 is injected intrasplenically. Typically, CT-26 tumor undergoes rapid growth in the spleen as well as the liver. Thus, tumor size and the weight of the spleen and liver are employed as rough estimates of the amount of tumor growth at the site of injection, *i.e.*, spleen, and metastatically, *i.e.*, liver. The data presented in Table 7 unequivocally demonstrates a striking effect of MTP-PE at levels that are not anti-neoplastic. The weight of the spleen and liver are nearly identical when the second neoplastic agent is administered at 50 mg/kg regardless of whether MTP-PE is also administered. Likewise, the tumor size in the spleen and the number of metastases in the liver are virtually the same. Therefore, the MTP-PE had

no additive anti-neoplastic effect. However, when the MTP-PE is administered with a second neoplastic agent known to be toxic at the administered dose, the treated mice not only survived, but appeared to experience greater tumor regression. The ameliorative effect of the MTP-PE on mucositis was also demonstrated in, *e.g.*, Examples 4 and 7 and Figure 20, where objective evidence was presented that mucositis was reduced or eliminated in mice receiving MTP-PE while being with an anti-neoplastic agent.

Applicants **strongly** disagree with the characterization of the teachings of the Kleinerman publications. Kleinerman 1989 fails to teach or suggest mucositis as a target for MTP-PE treatment to one of ordinary skill in the art of cancer biology. Kleinerman 1989 simply discloses the *in vitro* cytotoxicity and cytokine production profile of peripheral monocytes in patients receiving MTP-PE. Kleinerman neither expressly nor implicitly addresses the treatment of any side effect, or mucositis in particular, resulting from a neoplastic agent. Moreover, Kleinerman lacks any indication that patients with mucositis were included in the patient cohort. In the absence of such disclosure, the current scientific knowledge in the art fails to support the assumption that the patients inherently have mucositis. Thus, it cannot be considered inherent that such patients were included in the study.

Likewise, Kleinerman 1992 also fails to teach or suggest mucositis as a target for MTP-PE treatment to one of ordinary skill in the art of cancer biology. In this study, Kleinerman examines a cohort of patients characterized as disease-free, *i.e.*, have no detectable osteosarcoma. Again, Kleinerman is silent regarding the presence or absence of mucositis or other side effects in the patient cohort. Without more, the disclosure of Kleinerman cannot be construed to inherently include patients with mucositis.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 (b).

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 204372000901. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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